

Thiol/Disulfide homeostasis in childhood chronic kidney disease

Thiol/Disulphide homeostasis in chronic kidney disease

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Abstract

Aim: The pathogenesis of chronic kidney disease (CKD) remains unknown, but an imbalance between the oxidant and antioxidant defense systems may be a potent trigger of adverse effects in chronic kidney disease (CKD) patients. Measuring thiols in plasma offers an indirect marker of antioxidative defence. This study aimed to determine thiol/disulfide homeostasis as a new indicator of oxidant and antioxidant defence systems in pediatric CKD patients.

Material and Methods: This prospective case-control study included 50 pediatric CKD patients (34 non-dialyzed and 16 dialyzed) and 50 gender- and age-matched healthy controls.

Results: The native thiol, total thiol, and disulfide levels were significantly lower in the CKD group than in the control group ($p=0.003$, $p<0.001$, $p=0.002$, respectively). There was a significant correlation between the glomerular filtration rate, and the native thiol levels and total thiol levels ($p=0.003$, for each). The native and total thiol levels in the dialyzed patients were significantly lower than in the non-dialyzed patients ($p<0.001$, $p=0.002$, respectively).

Discussion: We observed that the levels of native thiol, total thiol and disulfide in pediatric CKD were lower than in healthy controls, indicating that low thiol levels might be an important factor in the pathogenesis of CKD.

Keywords

Children; Chronic kidney disease; Dialysis; Dynamic Thiol/Disulphide homeostasis; Oxidative stress

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Introduction

Chronic kidney disease (CKD) is an irreversible progression of systemic or primary renal diseases. Oxidative damage caused by increased oxidative stress and decreased antioxidant defence system is suggested to cause the progression of CKD and the development of kidney complications [1-3].

The oxidant and antioxidant defence systems imbalance and an increase in the production of free radicals maybe exacerbated by both hemodialysis and peritoneal dialysis [4-8].

Thiols are important components of antioxidant systems, which can be oxidized by one electron to form disulfide [-SS] bonds, which can again be reduced to thiol groups. This reversible reaction is important for maintaining dynamic thiol/disulfide homeostasis (DTDH) in the body. The total thiol level is indicative of both oxidized and reduced thiol forms, whereas the native thiol level is indicative of only the reduced thiol form. Under oxidative stress conditions, the level of native thiol decreases, while the disulfide concentration increases, but there is no change in the total thiol level [9].

The development of new diagnostic methods for detecting markers of oxidative stress may lead to a better understanding of the negative effects of oxidative stress on oxygenation and transport functions in renal cells [10,11]. Plasma thiol/disulfide homeostasis measurement is achieved with high accuracy and sensitiveness by determining native thiol and reducible dynamic disulfide, individually or together, using a novel method (colorimetric and spectrophotometric) developed by Erel and Neselioglu [9]. Thus, double-sided DTDH (antioxidant/oxidant) components can be easily measured.

The present study aimed to investigate DTDH as a new indicator of oxidative stress in pediatric CKD patients. To the best of our knowledge, this is the first-pilot study investigating dynamic thiol/disulfide homeostasis in pediatric CKD patients using a new method.

Material and Methods

Characteristics of Patients

This prospective case-control study was conducted at the tertiary hospital between January 2015 and July 2015. The study included 50 pediatric CKD patients and 50 age-, gender- and Body Mass Index (BMI)-matched healthy controls. The CKD group was divided into subgroups as dialyzed (hemodialysis [HD]: n=9; peritoneal dialysis [PD]: n=7) and non-dialyzed (n=34) patients. The exclusion criteria were as follows: (1) patients with evidence of acute infections, inflammatory disorders, malignancy; (2) patients with C-reactive protein (CRP) plasma levels > 3 mg/dL; (3) patients who receive HD therapy with a Kt/Vurea<1.4/week; (4) patients who receive PD therapy with a Kt/Vurea<1.7/week; (5) patients with peritonitis 3 months prior to enrolment. None of the healthy controls used an antioxidant agent (N-acetyl cysteine, allopurinol, vitamin supplements, or lipid-lowering medication), received medical or herbal therapy, or used cigarettes and alcohol.

All the HD patients were routinely dialyzed using polysulfone membrane dialyzers containing bicarbonate solutions for four hours a day, three times a week. Continuous ambulatory PD (CAPD) with solutions containing 1.36%-2.27% glucose was administered to all the PD patients.

CKD was defined as a decrease in the glomerular filtration rate (GFR) in this study. The estimated glomerular filtration rate (eGFR) was calculated using the Schwartz method, which is the most popular equation currently used in children [12].

Hypertension was defined as blood pressure >95th percentile for age, gender, and height, according to the Task Force Report on High Blood Pressure in Children and Adolescents criteria for casual BP recordings [13].

Height and weight were measured, and then BMI was calculated using the formula: BMI=kg/m².

The study protocol was approved by the Ethics Committee of Ankara Yıldırım Beyazıt University (Reference number: 201/02/03) and was performed in accordance with the principles of the Declaration of Helsinki and good clinical practices. Informed consent was obtained from the parents of all patients.

Dynamic Disulfide/Thiol Homeostasis Analysis

Venous blood samples were collected from all participants after fasting for 8 hours (at the start of the mid-day dialysis session in PD patients and at the start of the mid-week dialysis session in the HD patients). Routine laboratory parameters, including hemogram, biochemistry, and CRP levels, were measured in all the participants via standard laboratory techniques.

The samples for DTDH parameters (native thiol, total thiol, and disulfide levels, and the disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios) were centrifuged at 1500 g for 10 min, and stored at -80 °C until analysis. An automated chemistry analyzer (Shimadzu UV-1800 spectrophotometer) with a temperature-controlled cuvette holder and a Cobas c501 automated analyzer (Roche Diagnostics, Mannheim, Germany) were used to measure DTDH parameters as μmol/L [9]. DTDH was determined according to the native thiol and reducible dynamic disulfide levels. Subtracting the native thiol level from the total thiol level, and then dividing the difference by two provides the disulfide bond quantity. In addition, other related parameters (disulfide/total thiol, disulfide/native thiol, and native thiol/total thiol ratios) were calculated [9].

Before the advent of Erel and Neselioglu's novel measurement technique described herein and used in the present study, it was feasible to measure only low-molecular-weight compounds, which include a small portion of the body's thiol pool; therefore, the levels of thiol and disulfide measured using older methods may not precisely indicate the thiol/disulfide homeostasis status. Thiol/disulfide homeostasis can be creditably, separately, or collectively evaluated using this new method [9].

The CKD and control groups and the patient dialyzed subgroups were compared according to age, gender, CRP, native thiols, total thiols, disulfide, disulfide/native thiols, native thiols/total thiols, and disulfide/total thiols, all of which are parameters of thiol/disulfide homeostasis.

Statistical analysis

Statistical analysis was performed using SPSS for Windows v.15.0. (SPSS, Inc., Chicago, IL). Data are shown as mean ± SD, or median and range. The chi-square test was used to identify differences in categorical variables between groups. Student's t-test and the Mann-Whitney U test were used to compare numeric demographic variables, laboratory findings, and serum DTDH parameters between the CKD and control groups.

Correlations between thiol/disulfide homeostasis parameters and other clinical and laboratory findings that were normally distributed were determined using Pearson's correlation analysis. The level of statistical significance was set at $p < 0.05$.

Results

The mean age in the CKD group was 11.8 ± 5.2 years (median: 12; range: 0-18 years), versus 11.1 ± 4.4 years (median: 12; range: 1-18 years) in the control group. There were 47 girls (47%) and 53 boys (53%) in the study. There were no significant differences in age, gender, or BMI between the CKD and control groups ($p > 0.05$ for each). C-reactive protein (CRP) levels were normal in all the participants. The demographic data, clinical and laboratory findings, and thiol/disulfide homeostasis parameters in both groups are summarized in Table 1.

Table 1. The demographics, clinical and laboratory findings of study population.

Variables	CKD (n = 50)	Controls (n = 50)	p values
Age (years) (median 12)	11.8±5.2	11.1±4.4	0.481
Sex (females/males)	23/27	24/26	0.843
Body mass index (kg/m ²)	17.2±2.8	17.9±3.8	0.253
Systolic blood pressure mm/Hg	104.2±12.3	100.8±11.7	0.156
Diastolic blood pressure mm/Hg	66.0±8.3	66.7±9.9	0.704
Total Protein (g/l)	6.7±0.8	7.0±0.7	0.138
Albumin (g/dl)	3.9±0.6	4.4±0.3	<0.001*
Blood Urea Nitrogen (mg/dl)	49.0±30.8	10.5±3.5	<0.001*
Creatinine (mg/dl)	4.4±3.6	0.5±0.09	<0.001*
Uric Acid,	6.5±1.2	4.3±0.9	<0.001*
Hemoglobin (g/dl)	10.9±2.3	13.5±1.0	<0.001*
Platelet count	282.5±80.5	282.0±85.5	0.974
Native thiol (μmol/L)	314.0±101.7	376.9±103.9	0.003*
Total thiol (μmol/L)	357.9±109.2	434.5±99.0	<0.001*
Disulphide (μmol/L)	21.9±10.1	28.7±11.0	0.002*
Disulphide/native thiol (%)	7.8±5.1	9.5±8.6	0.242
Disulphide/total thiol (%)	6.5±3.3	7.3±4.6	0.298
Native thiol/total thiol (%)	86.9±6.7	85.2±9.2	0.298
GFR (ml/min/1.73m ²)	29.2±19.3	143.2±23.7	<0.001*

Abbreviations; CKD: Chronic kidney disease, GFR: glomerular filtration rate
* $p < 0.05$: Statistically significant

In the CKD group, albumin and hemoglobin levels, and the GFR were significantly lower, and blood urea nitrogen, creatinine, and uric acid levels were significantly higher than in the control group ($p < 0.001$ for each) (Table 1).

As shown in Table 2, there were no significant differences in age, gender, BMI, or total protein, albumin, and uric acid levels between the dialyzed and non-dialyzed CKD patients ($p > 0.05$ for each).

Native thiol, total thiol, and disulfide levels were significantly lower in the CKD group than in the control group ($p = 0.003$, $p < 0.001$, and $p = 0.002$, respectively) (Figure 1). The native thiol and total thiol levels were lower in the dialyzed CKD patients than in the non-dialyzed CKD patients ($p < 0.001$ and $p = 0.002$, respectively) (Figure 2). The DTDH parameters of the groups are shown in Figures 1 and 2.

Table 2. The demographics, clinical and laboratory findings of CKD group.

Variables	Non-dialyzed CKD (n = 34)	Dialyzed CKD (n = 16)	p values
Age (years)	11.4±5.2	12.7±5.5	0.094
Sex (females/males)	15/19	8/8	0.700
Body Mass Index (kg/m ²)	17.3±2.8	17.0±2.9	0.967
Systolic Blood Pressure mm/Hg	105.6±13.1	101.2±10.2	0.241
Diastolic Blood Pressure mm/Hg	67.7±9.7	64.3±10.4	0.051
Total Protein (g/l)	6.8±0.8	6.5±0.9	0.173
Albumin (g/dl)	4.0±0.5	3.7±0.6	0.049*
Blood Urea Nitrogen (mg/dl)	41.9±21.9	64.0±41.0	0.016*
Creatinine (mg/dl)	2.5±1.3	8.5±3.4	0.001*
Uric Acid	6.4±1.2	6.8±1.3	0.230
Hemoglobin (g/dl)	11.4±1.9	9.8±2.5	0.015*
Platelet count	284.2±81.8	279.0±80.1	0.835
Native thiol (μmol/L)	346.3±83.5	245.3±105.1	<0.001*
Total thiol (μmol/L)	390.3±92.8	289.1±112.2	0.002*
Disulphide (μmol/L)	21.9±11.2	21.9±7.5	0.980
Disulphide/native thiol (%)	6.5±3.3	10.8±6.8	0.004*
Disulphide/total thiol (%)	5.6±2.6	8.4±4.0	0.004*
Native thiol/total thiol (%)	88.7±5.2	83.0±8.0	0.004*
GFR (ml/min/1.73m ²)	37.9±17.6	10.7±2.7	<0.001*

Abbreviations; CKD: Chronic kidney disease, GFR: glomerular filtration rate
* $p < 0.05$: Statistically significant

Table 3. Findings related to thiol/disulfide hemostasis parameters in CKD group

Variables	Native thiol (μmol/L)		Total thiol (μmol/L)		Disulfide (μmol/L)		Disulfide/native thiol (%)		Disulfide/total thiol (%)		Native thiol/total thiol (%)	
	r	p	r	p	r	p	r	p	r	p	r	p
Age (years)	-0.097	0.501	-0.084	0.564	-0.045	0.759	-0.023	0.873	-0.023	0.873	0.023	0.873
BMI (kg/m ²)	-0.446	0.001*	-0.395	0.005*	-0.006	0.964	0.259	0.069	0.259	0.069	-0.259	0.069
Systolic BP	-0.200	0.163	-0.145	0.315	0.095	0.513	0.194	0.177	0.194	0.177	-0.194	0.177
Diastolic BP	-0.164	0.255	-0.139	0.337	-0.033	0.818	0.103	0.478	0.103	0.478	-0.103	0.478
Albumin (g/dl)	0.243	0.089	0.230	0.107	0.048	0.739	-0.199	0.165	-0.199	0.165	0.199	0.165
BUN (mg/dl)	-0.196	0.171	-0.176	0.222	0.016	0.912	0.254	0.075	0.254	0.075	-0.254	0.075
Creatinine (mg/dl)	-0.441	0.001*	-0.402	0.004*	-0.067	0.643	0.309	0.029*	0.309	0.029*	-0.309	0.029*
Uric Acid (mg/dl)	-0.284	0.046*	-0.285	0.045*	-0.342	0.015*	-0.132	0.361	-0.132	0.361	0.132	0.361
Platelet count	0.111	0.441	0.116	0.421	0.140	0.334	0.034	0.815	0.034	0.815	-0.034	0.815
Hemoglobin (g/dl)	0.231	0.107	0.229	0.109	0.023	0.877	-0.242	0.091	-0.242	0.091	0.242	0.091
GFR	0.413	0.003*	0.405	0.003*	0.119	0.409	-0.234	0.102	-0.234	0.102	0.234	0.102

Abbreviations; CKD: Chronic kidney disease, BMI: Body mass index, BP: Blood pressure, BUN: Blood Urea Nitrogen, GFR: Glomerular filtration rate
* $p < 0.05$: Statistically significant

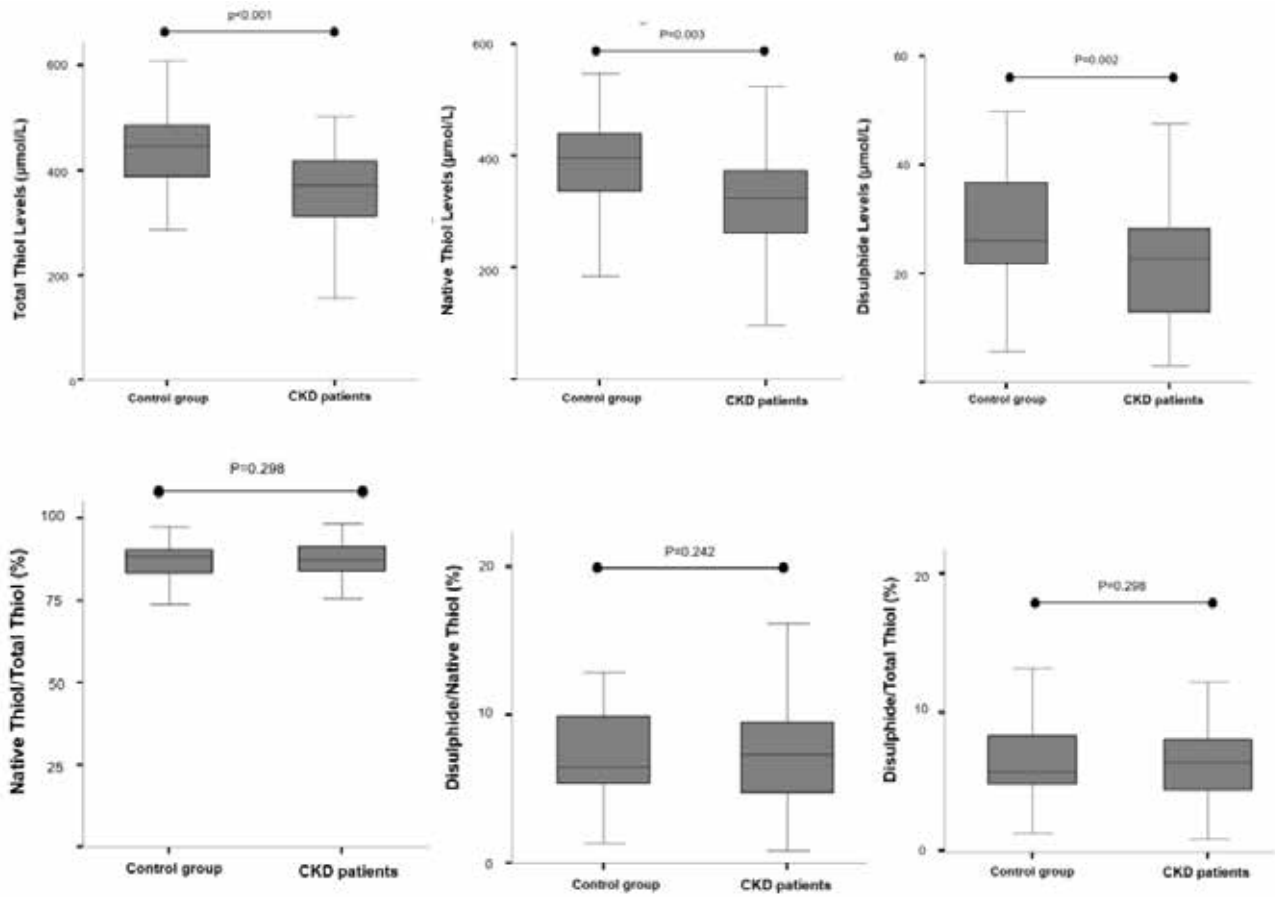


Figure 1. Comparison of the thiol/disulphide homeostasis parameters between CKD and control group
Abbreviation; CKD: chronic kidney disease

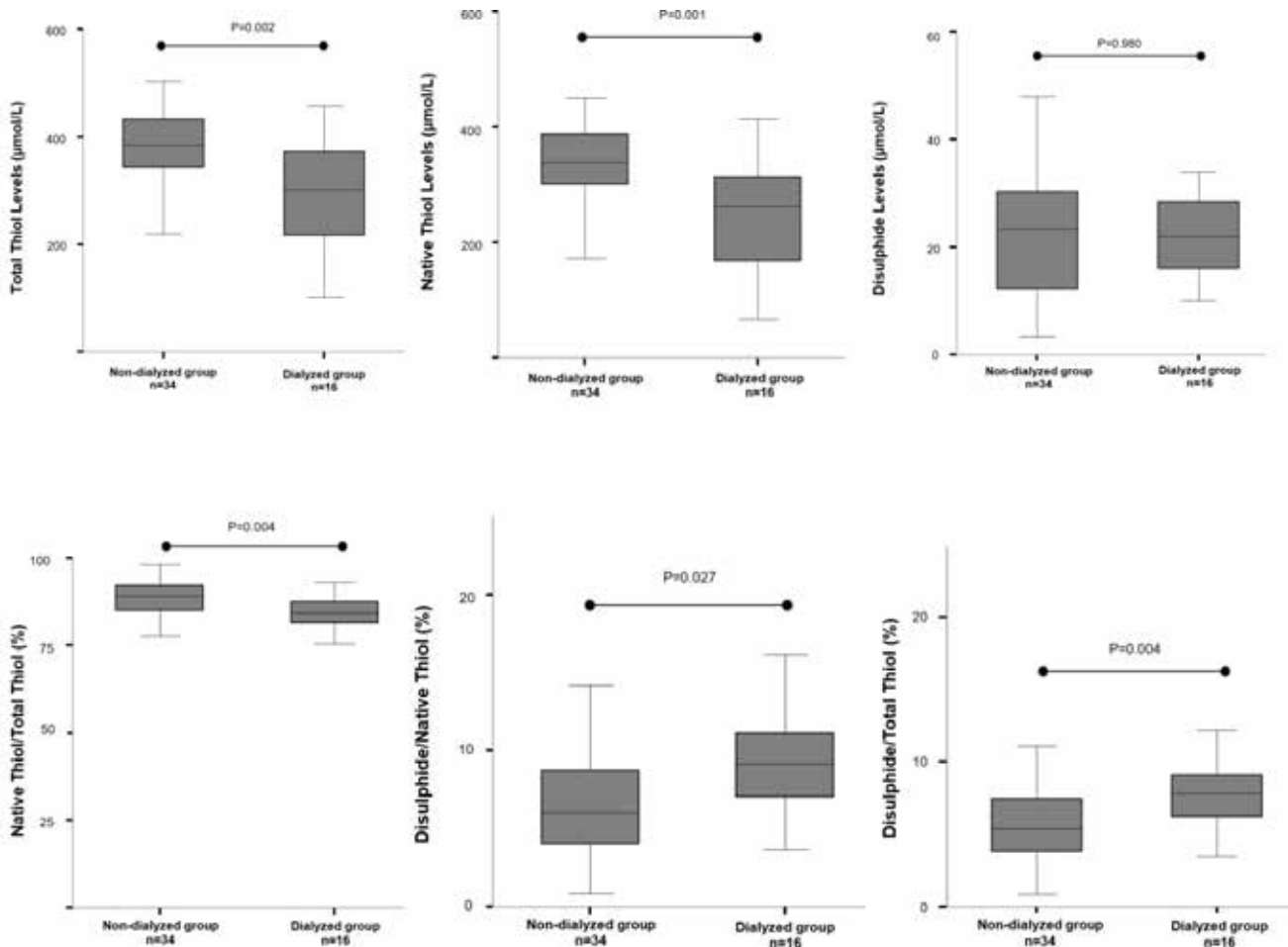


Figure 2. Comparison of the thiol/disulphide homeostasis parameters in CKD group

The native thiol and total thiol, disulfide levels were lower in patients with stage IV CKD than in patients with stage II and III CKD ($p=0.002$, $p=0.004$ respectively). A significant correlation was observed between uric acid and total thiol ($r=0.307$, $p=0.030$), and between uric acid and native thiol ($r=0.378$, $p=0.007$) in CKD. The native thiol levels were significantly lower in the PD patients than in the HD patients ($p=0.036$).

In the dialyzed and non-dialyzed CKD patients, there was a significant correlation between native thiol, disulfide and total thiol, and the GFR, creatinine, and uric acid levels (Table 3).

Discussion

The present study evaluated thiol/disulfide homeostasis in pediatric CKD patients using a novel automated method and found that the native thiol, total thiol, and disulfide levels were significantly lower in the CKD patients than in healthy controls. Our results indicated that not only the oxidative system, but also the antioxidant system is impaired in pediatric CKD patients, and that antioxidant levels decrease to a greater extent than oxidant levels (higher disulfide/native thiol and disulfide/total thiol ratios). The study's most unique finding is that the most severe oxidative stress imbalance was in peritoneal dialysis patients ($p=0.036$).

Earlier studies on adults have reported that plasma protein thiols decrease in patients with CKD, and that even in pre-dialysis CKD patients there is an increase in oxidative stress and a decrease in the antioxidant defence system (superoxide dismutase, glutathione peroxidase, catalase, vitamins E and C, and selenium) [3, 14-17].

The oxidative state is further exacerbated by dialysis [4-7]. In our study, the native thiol and total thiol levels and native thiol/total thiol ratios were lower in the dialyzed patients than in the non-dialyzed patients. This indicates that total thiols, in particular, are affected to a greater degree than native thiols in dialyzed patients.

The higher level of oxidative stress observed in the PD patients than in the HD patients in our study, is thought to possibly be due to an increase in the severity of uremia and inflammatory responses, or a decrease in the albumin level. It has been reported that the free fraction of thiols increased and the protein-related fraction decreased in PD patients [15]. A study on adults reported that the total thiol and native thiol levels were significantly lower in end-stage renal failure (ESRD) patients than in controls, and that the levels were lower in PD patients than in those undergoing other renal replacement therapies [14].

We found that the oxidant disulfide bond formation was significantly lower in the CKD group than in the control group, but there was no significant difference between non-dialyzed and dialyzed CKD patients. HD has been reported to have a positive effect on antioxidant homeostasis [7, 17-19]. The dialyzer membrane and HD treatment can play an important role not only in increasing Reactive oxygen species (ROS) formation, but also in ROS elimination, i.e. they can improve the oxidative state and reverse the increase in oxygen radical production in the blood of ESRD patients [7]. This might be the reason that disulfide level was not significantly different, despite the observed decreases in the native thiol and total

thiol levels in our HD and PD patients.

In our study, a positive correlation was found between the GFR, and native thiol and total thiol levels in the CKD patients. In addition, the native thiol and total thiol levels decreased in the pediatric CKD patients as the GFR decreased. These results indicate that uremic patients may not respond adequately to oxidative stress. It has been reported that the severity of uremia, rather than dialysis treatment, contributes significantly to oxidative stress in both dialyzed and non-dialyzed CKD patients [18, 20-23]. Our findings are in agreement with the literature.

Ateş et al. [24] observed that the total thiol level was significantly lower in patients with primary hypertension than in healthy controls.

Our study has some limitations. One of these was the lack of analysis of other markers of oxidative stress that might affect thiol redox status. Other limitations are that the CKD group was heterogeneous. Lastly, the study population included a relatively small number of patients, in particular dialyzed patients. Despite these limitations, the fact that this was a pilot study will contribute to the literature.

To the best of our knowledge, the present study is the first to investigate the effects of oxidative status in non-dialyzed and dialyzed pediatric CKD patients based on analysis of DTDH. Our findings suggest that the decrease in native and total thiol levels in dialyzed CKD patients was greater than in the non-dialyzed patients, but the disulfide levels did not differ significantly between CKD patient subgroups. Given the effects of oxidative stress on the progression of CKD, early detection and correction of oxidative processes may help prevent the progression of CKD and reverse its pathophysiology. This new method might be suitable for large-scale clinical trials and can be used as a useful indicator method of oxidative stress in routine screening. Since this is a pilot study on this subject, our study is very important.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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